Update on Diabetes Mellitus Treatment: Targeting the Incretin System
Overview

• Underlying defects with Type 2 diabetes
• Importance of managing postprandial glucose control
• Amylin
• Incretin Hormones
  – New therapies that target incretin hormones
The Diabetes Epidemic

- 7.0% of US children and adults have diabetes.
- 54 million have pre-diabetes
- 1.5 million new cases diagnosed in people aged 20 years or older in 2005.
- 90-95% Type 2

Prevalence of Diabetes in the U.S., 2005

National Diabetes Surveillance System
Insulin and Glucagon Regulate Normal Glucose Homeostasis

Glucagon (alpha cell) 
Insulin (beta cell)
Pancreas

Fasting State

Glucose output
Liver

Blood glucose

Glucose uptake
Muscle Adipose tissue

Insulin and Glucagon Regulate Normal Glucose Homeostasis

Blood glucose

Glucose output

Glucose uptake

Fed state

Pancreas

Insulin (beta cell)

Glucagon (alpha cell)

Liver

Muscle

Adipose tissue

Case Study

• June is 47-year-old woman who signs up for glucose screening in your pharmacy.
• Medical History: gestational diabetes 13 yrs ago with only child, hypothyroidism, occasional vaginal yeast infections
• Medications: levothyroxine 0.1 mg/day
• Family History: 70-year-old father developed type 2 diabetes at age 58
• Fasting glucose = 105 mg/dl
• HT: 5'6”, WT: 188 lbs  (BMI: 30.3)
• BP: 142/86 mm Hg
Natural History of Type 2 Diabetes

Prediabetes/IGT/IFG  T2DM

Glucose

Postprandial glucose
Fasting glucose

126 mg/dl

Relative Function

Insulin resistance — hepatic and peripheral
Insulin level
Beta-cell function

100%

Years from Diabetes Diagnosis

-10  -5  0  5  10  15  20  25  30

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IGT=impaired glucose tolerance; IFG=impaired fasting glucose.

Major Pathophysiologic Defects in Type 2 Diabetes

- Insulin resistance
- Glucose uptake
- Hepatic glucose output
- Islet-cell dysfunction
- Insulin (beta cell)
- Glucagon (alpha cell)
- Hyperglycemia

Liver

Muscle

Adipose tissue

What are the fundamental defects in Type 2 diabetes?

- Relative lack of insulin
  - Early in disease → insulin resistance
  - Later → combination of insulin resistance and declining insulin secretion
  - Late → failure of beta cells
- Accelerated gastric emptying
- Unsuppressed postprandial glucagon secretion
- Impaired meal-stimulated insulin release (deficient amylin and GLP-1 secretion)
Gastric Emptying Rates

*P=0.0005, †P <0.05

Type 2 Diabetes: A Disease of Deficient Appetite Signals?

B-cell defect

Reduced neuronal insulin/leptin action

Reduced GLP-1 and amylin

Positive energy balance

Food intake

Energy expenditure

Type 2 Diabetes

Insulin Resistance

Prevalence of Overweight in the U.S., 2006
Welcome to Texas

"Come for the BBQ - stay for the angioplasty"
Unmet Pathophysiologic Needs in Type 2 Diabetes Mellitus

• Progressive loss of beta-cell function and mass
• Inappropriate glucagon secretion
• Uncontrolled postprandial hyperglycemia
• Possible impaired satiety signals resulting in weight gain
• Accelerated gastric emptying
• Deficient incretin effect
Case Study

• Based on her risk for Type 2 diabetes and elevated fasting level, June was referred to her PCP
• Lab results:
  – 2-hour postmeal glucose = 158 mg/dL
• Consultation with dietitian
• Starts lifestyle modification program (weight loss and walking 30 mins 3x/wk)
## Current Treatment Guidelines

<table>
<thead>
<tr>
<th>Biochemical Index</th>
<th>Normal</th>
<th>ADA Goal</th>
<th>ACE/AACE Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting/preprandial plasma glucose (mg/dl)</td>
<td>&lt; 100</td>
<td>90-130</td>
<td>≤ 110</td>
</tr>
<tr>
<td>Postprandial plasma glucose (mg/dl)</td>
<td>&lt; 140</td>
<td>&lt; 180</td>
<td>≤ 140</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>&lt; 6</td>
<td>&lt; 7</td>
<td>≤ 6.5</td>
</tr>
</tbody>
</table>

ADA = American Diabetes Association  
ACE/AACE = American College of Endocrinology/American Association of Clinical Endocrinologists  
*Diabetes Care* 2006;29(suppl 1):S4-S42.  
What is A1C and Why is it Important?

• Glycated or glycosylated hemoglobin
  – HbA1C, A1C
• Normal range: 4.0% to 6.7%
• Reflects mean glucose levels over preceding 120 days
• Elevated in: Uncontrolled diabetes mellitus, lead toxicity, alcoholism, iron deficiency anemia, hypertriglyceridermia
GOOD GLYCEMIC CONTROL: A CRITICAL GOAL

• Each 1% reduction in mean A1C
  – Reduces risk of death from diabetes by 21%
  – Reduces risk of heart attack by 14%
  – Reduces risk of microvascular complications by 37%

UKPDS 35 BMJ 2000:321:405-412
GOOD GLYCEMIC CONTROL: A CRITICAL BUT ELUSIVE GOAL

A1C Goal Achievement

- 36% > 7%
- 64% < 7%

GOOD GLYCEMIC CONTROL: A CRITICAL BUT ELUSIVE GOAL

• Multiple factors continue to challenge goal achievement.
  – natural progression of beta-cell dysfunction with increasing hyperglycemia
  – lack of long-term success with diet and exercise
  – poor adherence to prescribed therapy
  – uncontrolled post-prandial glucose
Both FPG and PPG Contribute to Elevated A1C Levels


Increasing Contribution of PPG as A1C Improves

FPG = fasting plasma glucose
PPG = post prandial glucose

Diabetes Care 2003;26:881-885.
Relationship between A1C Baseline and Reduction With Pharmacologic Intervention

<table>
<thead>
<tr>
<th>Baseline A1C%</th>
<th>6.0–6.9</th>
<th>7.0–7.9</th>
<th>8.0–8.9</th>
<th>9.0–9.9</th>
<th>10.0–11.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients enrolled in clinical trials</td>
<td>n=410</td>
<td>n=1,620</td>
<td>n=5,269</td>
<td>n=1,228</td>
<td>n=266</td>
</tr>
</tbody>
</table>

Importance of Postprandial Hyperglycemia

- IGT is a risk factor for cardiovascular disease
- Contributes more to A1C than FPG at A1Cs < 7.3%
- Can be rate limiting factor for achieving adequate glycemic control

*Diabetologia* 2002;45:1224-1230
*Diabetes Care* 1999;22:920-924
### Treatments for Type 2 Diabetes

<table>
<thead>
<tr>
<th><strong>Increase insulin responsiveness</strong></th>
<th><strong>Modify intestinal absorption of carbohydrate</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Biguanides</td>
<td>• Alpha-glucosidase inhibitor</td>
</tr>
<tr>
<td>- Metformin (Glucophage®, Fortamet®)</td>
<td>- Acarbose (Precose®)</td>
</tr>
<tr>
<td>• Thiazolidinediones</td>
<td>- Miglitol (Glyset®)</td>
</tr>
<tr>
<td>- Rosiglitazone (Avandia®)</td>
<td></td>
</tr>
<tr>
<td>- Pioglitazone (Actos®)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Stimulate insulin release</strong></th>
<th><strong>Reduce postprandial glucose</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sulfonylureas</td>
<td>• Amylin Analog</td>
</tr>
<tr>
<td>- Glipizide (Glucotrol®, glipizide XL (Glucotrol XL®))</td>
<td>- Pramlintide (Symlin®)</td>
</tr>
<tr>
<td>- Glyburide (DiaBeta®, Glynase®, Micronase®)</td>
<td>• Incretin mimetics</td>
</tr>
<tr>
<td>- Glimepiride (Amaryl®)</td>
<td>- Exenatide (Byetta®)</td>
</tr>
<tr>
<td>• Meglitinides</td>
<td>- Sitagliptin (Januvia®)</td>
</tr>
<tr>
<td>- Nateglinide (Starlix®)</td>
<td>- Vildagliptin (Galvus®)</td>
</tr>
<tr>
<td>- Repaglinide (Prandin®)</td>
<td></td>
</tr>
</tbody>
</table>

| **Correct Insulin Deficiency**      |                                              |
|-------------------------------------|                                              |
| • Insulin                           |                                              |
Amylin

• Works in conjunction with insulin to help control blood glucose levels
• A neuroendocrine hormone that is cosecreted by the beta cells of the pancreas in response to food intake.
• Regulates glucose appearance in the bloodstream from the stomach and liver.
Pramlintide (Symlin®)

- Synthetic analog of human amylin for postprandial control of glucose
- Slows gastric emptying, suppresses postprandial glucagon secretion and modulates appetite by enhancing satiety
- Indicated in Type 2 diabetes
  - adjunct treatment to mealtime insulin with or without a concurrent sulfonylurea agent and/or metformin
Pramlintide (Symlin®)

- Given SC with major meals
- Advantage
  - Weight loss of ~1-1.5 kg over 6 months
  - Decreases HbA1c by 0.5-0.7%
- Disadvantage
  - ADE: hypoglycemia, nausea (50%), headache
  - Contraindication: gastroparesis
  - Slows the absorption of oral medications
- Important to lower mealtime insulin dose 50% when start this agent
Incretin Hormones

• Peptides produced by GI tract in response to food
• Influence post-prandial insulin release (insulinotropic)
• Glucagon-like peptide-1 (GLP-1)
• Gastric inhibitory polypeptide (GIP)
The Incretin Effect – Beta Cell Response to Oral Glucose

GLP-1 Secretion and Metabolism

Mixed Meal

Intestinal GLP-1 release

GLP-1 (7-36)
Active

DPP-IV

Rapid Inactivation (>80% of pool)

GLP-1 (9-36)
Inactive

Plasma

GLP-1 (7-36)
Active

GLP-1 Actions

Renal Clearance

DPP = dipeptidyl peptidase

GLP-1 Actions

- Stimulates glucose dependent insulin secretion
- Slows gastric emptying
- Suppresses postprandial glucagon secretion
- Reduces food intake
- May improve insulin sensitivity
- *In vitro* stimulates beta-cell proliferation
Postprandial GLP-1 Levels

NGT = normal glucose tolerance
IGT = impaired glucose tolerance
T2DM = type 2 diabetes mellitus

J Clin Endocrinol Metab. 2001;86(8):3853-60.
Dipeptidyl Peptidase IV (DPP-IV)

- Lymphocyte cell surface protein CD26
- Enzyme that rapidly inactivates GLP-1
- Inhibition of DPP-IV enhances activity of GLP-1 and other bioactive peptides (GIP, PACAP38, GRP)
  - Stimulates release of insulin
  - Reduces secretion of glucagon
GLP-1 Secretion and Metabolism

Mixed Meal

Intestinal GLP-1 release

GLP-1 (7-36)
Active

DPP-IV

GLP-1 (9-36)
Inactive

Plasma

GLP-1 (7-36)
Active

GLP-1 Actions

Renal Clearance

DPP = dipeptidyl peptidase

Incretin-Based Therapies

• Incretin Mimetics (GLP-1 agonists/analogs)
  – Exenatide (Byetta)
  – Others: Liraglutide, LY307161 SR, CJC-1131, ZP10, BIM51077

• Incretin Enhancers (DPP-IV inhibitors)
  – Sitagliptin
  – Vildagliptin
  – Others: saxagliptin
Exenatide (Byetta®)

• Binds to GLP-1 receptor
• T1/2 ~ 2.5 hrs
• Given as 5 – 10 mcg SC within 1 hr before morning and evening meal
• Indicated for type 2 patients not controlled on metformin, sulfonylurea, TZD, or combination
• Long acting formulation under development
Effects of Exenatide on Postprandial Glucose

J Clin Endocrinol Metab 2003;88:3082-3089
Exenatide

• Drug Interactions
  – Take oral contraceptives and antibiotics 1 hr before
  – ? take all medications 1 hr before or with meal when drug is not given

• Adverse effects
  – Nausea (50%), diarrhea, dyspepsia
  – Hypoglycemia can occur when given with sulfonylureas
What to Do About Nausea?

• Tends to improve over time
• May be less severe if exenatide is given closer to a meal
• Low-fat diet and eating slowly seem to help
• Remind patient to stop eating when full
Exenatide

• Advantages
  – Does not caused hypoglycemia unless combined with unadjusted doses of other hypoglycemics
  – Weight loss of ~ 4-6 lbs over 6 months, > 10 lbs over 2 years
  – Decreases A1C by 0.5-1%

• Disadvantages
  – ADE: diarrhea, dyspepsia, nausea, vomiting
  – Injection administration only
  – Administer within 60 minutes before meals
  – Concurrent use with insulin, meglitinides, or α-glucosidase is not well studied
Investigational GLP-1 Analogues

• Liraglutide
  – Long-acting, acylated GLP-1 analogue
  – t1/2 ~ 12-14 hrs
  – Once daily SC injection
  – Modest weight loss
**A1C Reduction with Liraglutide**

![Graph showing A1C reduction with Liraglutide](image)

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo adjusted Δ in A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide 0.6 mg</td>
<td>-0.9</td>
</tr>
<tr>
<td>Liraglutide 0.75 mg</td>
<td>-0.7</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

* P < 0.001 vs placebo

*Diabetes Care* 2004;27:1335-1342

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Sitagliptin (Januvia®)

• Orally active, selective inhibitor for the DPP-IV enzyme
• T1/2 ~ 12.4 hrs
• A1C effect: ↓ 0.65 - 0.8%
• Oral dosing: 50 - 100 mg once daily
  – can be administered with or without food
Placebo-Adjusted Results in a 24-Week Study of Sitagliptin

**A1C**
- Mean Baseline: 8.0%
- $P<0.001^*$
- $-0.8^+$
- $n=229$
- (95% CI: $-1.0, -0.6$)

**FPG**
- Mean Baseline: 170 mg/dL
- $P<0.001^*$
- $-17^+$
- $n=234$
- (95% CI: $-24, -10$)

**2-hr PPG**
- Mean Baseline: 257 mg/dL
- $P<0.001^*$
- $-47^+$
- $n=201$
- (95% CI: $-59, -34$)

*Compared with placebo.
$^+$Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
$^\ddagger$Difference from placebo.

Data from package insert

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Sitagliptin Indications

• Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus

• To improve glycemic control in combination with metformin or a PPARγ agonist (e.g., thiazolidinediones) when the single agent alone with diet and exercise does not provide adequate glycemic control

• Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis
Dosage

• Normal renal function or mild dysfunction
  – 100 mg daily

• Moderate to severe renal insufficiency

<table>
<thead>
<tr>
<th>50 mg once daily</th>
<th>25 mg once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate</strong></td>
<td><strong>Severe and ESRD‡</strong></td>
</tr>
</tbody>
</table>
| CrCl ≥30 to <50 mL/min (~Serum Cr levels [mg/dL]
  Men: >1.7–≤3.0; Women: >1.5–≤2.5) | CrCl <30 mL/min (~Serum Cr levels [mg/dL]
  Men: >3.0; Women: >2.5) |

‡ESRD = end-stage renal disease requiring hemodialysis or peritoneal dialysis.
Sitagliptin

• Drug Interactions
  – No known clinically meaningful drug interactions
  – Based on in vitro data, sitagliptin does not inhibit CYP isoenzymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19, or 2B6 or induce CYP3A4
Sitagliptin

• Adverse Effects
  – Premarketing – equal to placebo
  – Sitagliptin 100 mg versus placebo
    • Hypoglycemia (1.2% vs 0.9%)
    • Abdominal pain (2.3%, 2.1%)
    • Nausea (1.4%, 0.6%)
    • Diarrhea (3.0%, 2.3%)
Sitagliptin

• Advantages
  – No known drug interactions
  – Studied as monotherapy and in combination with glitazones, glipizide, and metformin
  – Available in combination with metformin (Janumet®)
    • 50mg/500mg & 50/1000
  – Weight neutral
  – Low rate of side effects
  – Low risk of hypoglycemia

• Disadvantages
  – Concurrent use with insulin, meglitinides, or α-glucosidase is not well studied
Vildagliptin (Galvus®)

- Indication: ? Most likely will be similar to sitagliptin
- A1C effect: ↓ 0.5 - 0.8%
- Oral dosing: 50-100 mg once daily
- Adverse effects: ? similar to placebo
- Effect on weight: 0 → -1.5 kg
- No known drug interactions
- Studied as monotherapy and in combination with glitazones, glimepiride, metformin, and insulin

A1C Reduction with Vildagliptin

- Placebo (n=55): -0.13%
- Vildagliptin 50 mg (n=52): -0.56%
- Vildagliptin 100 mg (n=60): -0.53%
Greatest Potential Limitation of DPP-IV Inhibitors

- DPP-IV is ubiquitous
- Nonspecific inhibition may increase neuropeptide Y, endomorphin peptide YY, growth hormone-releasing hormone, glucagon-like peptide 2, and other chemokines
- Effect on immune system appears positive or neutral
GLP-1 Mimetics versus DPP-IV Inhibitors

- No head-to-head comparisons
- Injectable vs. oral
- BID vs. QD
- Greater risk of hypoglycemia with mimetics
- More weight loss with mimetics
- DPP-IV agents appear better tolerated (less nausea)
- Similar impact on A1C
Incretin Agents

• Restore glucose-dependent insulin secretion in face of ingested nutrients
• Suppress glucagon levels to restore appropriate balance
• Potential to preserve beta cell function
Who might benefit most from incretin based therapy?

• Overweight or obese patient
  – rather than add an agent which may cause additional weight gain

• Uncontrolled on current therapy
  – Especially those close to A1C goal

• ? Early in disease to preserve beta cells
Case Study

• June is now on
  – glyburide 10 mg bid
  – metformin 1000 mg bid
• A1C = 7.2%
• She lost 10 lbs with lifestyle changes but has regained this plus another 5 lbs since on glyburide.
Dual Alpha-Gamma PPAR Agonists

• PPAR
  – Proliferator-Activated Receptor
  – Members of the larger steroid hormone nuclear receptor family

• Thiazolidinediones → PPAR-gamma agonists

• Fibrates → PPAR-alpha agonists

• Alpha/gamma agonists → lipid lowering and insulin sensitizing effects
Dual PPAR Agonists

• Development stopped
  – muraglitazar (Pargluva)
  – farglitazar
  – tesaglitazar (Galida)
  – ragaglitazar
  – TAK 559

• Still in the pipeline
  – GSK 590735, 501516, 677954
  – TAK 654
  – AZD6610
To Sum It All Up

• Incretin hormones have important role in Type 2 disease and management
• Incretin agents stimulate glucose dependent insulin secretion, slow gastric emptying, suppress postprandial glucagon levels, and decrease liver glucose release
• Agents are agonists or DPP-IV inhibitors
• Exenatide and sitagliptin on market
• Similar efficacy and side effect profile in Phase III testing of gliptins
• Many more incretin agents are waiting in the wings
May I be excused? My brain is full.